CLINICAL STUDY

The role of selective venous sampling in the management of persistent hyperparathyroidism revisited

Janneke E Witteveen¹, Job Kievit², Arian R van Erkel³, Hans Morreau⁴, Johannes A Romijn¹ and Neveen A T Hamdy¹

Departments of ¹Endocrinology and Metabolic Diseases, ²Surgery, ³Radiology and ⁴Pathology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands

(Correspondence should be addressed to N A T Hamdy; Email: n.a.t.hamdy@lumc.nl)

Abstract

Introduction: Localization studies are mandatory prior to revision surgery in patients with persistent hyperparathyroidism in order to improve surgical outcome and reduce the risk of lengthy explorations. However, in this case, noninvasive localization studies are reported to have a poor sensitivity. The aim of our study is to determine the accuracy of selective venous sampling (SVS) for parathyroid hormone (PTH) in localizing residual hyperactive parathyroid glands in patients with persistent or recurrent hyperparathyroidism.

Patients and methods: We retrospectively evaluated the localizing accuracy of 20 PTH SVS performed prior to revision surgery in 18 patients with persistent or recurrent primary hyperparathyroidism ($n=11$) or autonomous (tertiary) hyperparathyroidism ($n=7$). Tc99m-methoxy-isobutyl-isonitrile (MIBI)-single photon emission computed tomography (SPECT) was also performed in all patients prior to revision surgery. Operative and pathological data were obtained from hospital records.

Results: The SVS was able to accurately localize 15 of the 20 pathological glands removed at revision surgery, representing a sensitivity of 75%. This sensitivity is significantly higher than that of Tc99m-MIBI-SPECT, which was only 30% ($P=0.012$).

Conclusion: Our findings demonstrate that SVS is a valuable localization study in patients with persistent or recurrent hyperparathyroidism, with a sensitivity significantly higher than that of Tc99m-MIBI-SPECT. Our data suggest that SVS represents a useful addition to the preoperative workup of these patients prior to revision surgery.

European Journal of Endocrinology 163 945–952

Introduction

In primary hyperparathyroidism (PHPT), parathyroidectomy is reported to have a cure rate of 94–100% (1–10) with a complication rate of 0–2.7% in the hands of experienced surgeons (3, 5, 7–9). In contrast, revision surgery for persistent hyperparathyroidism poses a far greater challenge due to distortion and scarring of surgical planes caused by previous interventions. In addition, the likelihood of supernumerary parathyroid glands, ectopic localizations, and parathyromatosis (inadvertent seeding of parathyroid cells during previous surgeries) is also increased. For these reasons, pre-operative localization studies are highly recommended prior to revision surgery for persistent hyperparathyroidism in order to decrease the operating time, improve the surgical outcome, and reduce the risk of complications due to lengthy explorations (10–14). However, localizing residual hyperactive parathyroid tissue often represents an elusive task, particularly following

previous surgery for PHPT. The most widely used localization study, Tc99m-methoxy-isobutyl-isonitrile (MIBI)-single photon emission computed tomography (SPECT), has indeed been shown to hold significant limitations prior to revision surgery for persistent PHPT. Explanations for the poor localizing ability of Tc99m-MIBI-SPECT in persistent PHPT, as low as 50%, include the small size of residual pathological glands, higher probability of hyperplasia, and the potential distortion of the vascular supply to the residual hyperactive glands due to previous surgery (15–19).

Selective venous sampling (SVS) of parathyroid hormone (PTH) has been shown to be valuable in localizing hyperactive parathyroid glands (20–22), but this invasive technique has generally fallen out of favor since the introduction of noninvasive radionuclide tests, initially thallium–technetium subtraction scanning (23), and subsequently the more sensitive Tc99m-MIBI-SPECT (10). The diagnostic value of SVS is based on the assumption that the regional drainage of each

one of the four parathyroid glands is into the adjacent superior, middle, and inferior thyroid veins respectively (20). Despite potential anatomical variations, SVS is successful in predicting the side of a pathological parathyroid gland in 39–93% of patients with PHPT (20–22, 24–31) and, more importantly, in 66–75% of patients with negative noninvasive studies (21, 27, 32). The major limitation of SVS, however, is that it pinpoints the area of venous drainage of a hyperactive gland rather than its exact anatomical location. There may indeed be many variations in regional venous anatomy of the parathyroids due to embryological differences. Although each parathyroid gland thus tends to drain ipsilaterally and inferiorly, contralateral drainage has also been described (20). Variations in regional venous drainage may also occur as a result of previous surgical interventions, usually due to ligation of draining veins. In previously published studies, the predictive value of SVS was judged to be positive when a positive gradient was documented on the side of the neck where a pathological gland was found at subsequent surgery (15, 27, 29). The aim of this study is to evaluate whether SVS for PTH could contribute to a more accurate preoperative localization of residual hyperactive parathyroid tissue in patients with persistent hyperparathyroidism.

Patients

Using our hospital records, we selected all patients who had undergone Tc99m-MIBI-SPECT and SVS for PTH prior to revision surgery for persistent or recurrent PHPT or autonomous tertiary hyperparathyroidism (THPT) due to end-stage renal failure between February 1994 and January 2009. Eighteen patients who had undergone a total of 20 revision surgeries were considered eligible and were included in the study. Fifteen of the 18 patients (83%) had their initial parathyroidectomy at another hospital and were referred to our hospital for revision surgery. All revision surgeries were undertaken by two surgeons with considerable experience in endocrine surgery.

Methods

Demographic data, operative data, and pre- and post-operative laboratory data were obtained from patients' hospital records. All Tc99m-MIBI-SPECT scans were reviewed by an experienced nuclear medicine physician, blinded to the outcome of the subsequent revision surgery.

In our study, cure was defined as sustained normal serum calcium and PTH concentrations more than 6 months after parathyroidectomy (33). Persistent hyperparathyroidism was defined as persistently elevated serum calcium and PTH concentrations in consecutive samples within and beyond 6 months after surgery (33).

Parathyroid SVS technique

Parathyroid venous sampling was performed by an experienced intervention radiologist as follows: a 5 Fr MP catheter, with a selective end hole, was introduced via a sheath in the right femoral vein under local anesthesia and guided by fluoroscopy to each of the jugular, subclavian, brachiocephalic, and azygos veins and to the vena cava superior and inferior. Blood samples were obtained from several levels along these veins at close distances (1–2 cm), covering the venous drainage of normal anatomical locations as well as potential ectopic locations of the parathyroid glands. A total of 30–40 blood samples were collected in whole blood tubes with spray-coated potassium EDTA and were immediately put on ice before transportation to the laboratory for PTH measurement. The various sampling sites and any anatomical variation in the venous drainage system found at the time of sampling by injecting contrast (Iomeron 300, Bracco Imaging, Konstanz, Germany) were accurately recorded during the procedure.

At the end of the procedure, the catheter was withdrawn and pressure was applied at the point of entry in the femoral vein for ~10 min until hemostasis was achieved. Regular checks were undertaken for the following 1–2 h after which the patient was discharged home.

Blood samples were centrifuged and the separated serum was assayed in one batch using an immunochemiluminescent assay (Immulite 2500, Siemens, Deerfield, IL, USA). Using this assay, the normal range of serum iPTH concentration was 1.5–8 pmol/l. The measured PTH concentrations were plotted at the corresponding anatomical sites on the sampling map (Fig. 1).

Laboratory screening before the procedure included a coagulation screen and evaluation of renal and thyroid function to establish the safety of contrast administration. If anticoagulation was used, this was temporarily reversed and wherever possible NSAIDs and acetylsalicyl acid were discontinued for a few days before the procedure.

Similar to other venous catheterization procedures, potential complications of SVS include hematoma formation, venous thrombosis, perforation of blood vessels, pseudo-aneurysm, wound infection, and side effects of use of contrast material including anaphylactic reactions and deterioration of renal function (20, 34). Patients with a glomerular filtration rate of <45 ml/min who underwent SVS were prehydrated using normal 0.9% saline solution.

An SVS for PTH was deemed to be positive when a gradient of >50% was found between PTH concentrations at a specific anatomical site of sample collection compared with peripheral blood samples obtained at the time of procedure (17, 21).

For the purpose of the study, data of each SVS were reanalyzed by an experienced endocrinologist, blinded to the previously predicted localization and to the outcome of the surgical procedure.

Figure 1 PTH concentrations (pmol/l) plotted on the sampling map demonstrating a gradient in the brachiocephalic vein, the superior vena cava, and the azygos vein, suggesting a pathological parathyroid gland in the mediastinum, which corresponded to the subsequent operative finding of a pathological parathyroid gland in aorto-pulmonary window (shaded area).

Noninvasive preoperative localization studies

The Tc99m-MIBI-SPECT scan was performed as follows: following i.v. injection of 500 MBq of Tc99m-MIBI, planar images of the head and neck region and chest were performed at a matrix size of 256×256 (10 min per frame). Scintigraphy was performed as a dual-phase single tracer examination before each of the 20 revision surgeries. Images were acquired in the supine position, 15 min and 2 h after the injection of the radiopharmaceutical. A gamma camera (Toshiba GCA-7200, Tokyo, Japan) equipped with low-energy high-resolution collimators was used for image acquisition. SPECT was performed in a 128×128 matrix size, using a step angle of 4° and a step time of 35 s per step, 90 min after the injection. The filtered back projection was used for image reconstruction, using a Butterworth filter (8 order, subset 12).

Analysis of data

For the purpose of the analysis, the neck was divided into five designated anatomical areas: four thyroid quadrants, and a fifth 'elsewhere' area combining all possible ectopic localizations in the mediastinum (Fig. 2). A true-positive region was defined as a region from which a pathological parathyroid gland was removed at surgery, and in which the presence of the hyperactive parathyroid tissue was suggested in the same region by the preoperative localization test. A true-negative region was defined as a region in which no pathological parathyroid gland was found at surgery, and in which no presence of the hyperactive parathyroid tissue was suggested in this region by the preoperative localization test. A false-positive region was defined as a region in which no pathological parathyroid gland was found at surgery, although the presence of hyperactive parathyroid tissue was suggested in this region by the preoperative localization test. A false-negative region was defined as a region from which a pathological parathyroid gland was removed at surgery, although no presence of the hyperactive parathyroid tissue was suggested in this region by the preoperative localization test.

Figure 2 Analysis of the ability of SVS and Tc99m-MIBI-SPECT scan to correctly localize a pathological parathyroid gland as confirmed by localization at surgery by dividing the neck into five anatomical areas (the four thyroid quadrants and a 5th area of all possible ectopic localizations in the mediastinum).

True-negative and false-positive scans, sides, or regions could only be determined in patients who were cured after the surgery by the finding and removal of a pathological parathyroid gland elsewhere in the neck or mediastinum (this latter condition precluded compromising the sensitivity and specificity by false-negative surgery).

Widely accepted definitions for sensitivity and specificity were used. Sensitivity was thus judged to be the power of the test to identify the presence of pathological parathyroid glands in an exact region of neck. Specificity was judged to be the power of the test to recognize the absence of a pathological parathyroid gland in an exact region of the neck.

Statistical analysis

Statistical analysis was performed using the SPSS 16 software (SPSS Inc., Chicago, IL, USA). Results are expressed as mean $\pm$ s.e.m. unless otherwise stated. The McNemar test was used to assess the difference in localization accuracy between the SVS and Tc99m-MIBI-SPECT scan. A probability level of random difference of $P < 0.05$ was considered to be significant.

Ethical consideration

The methods used in this study were part of the clinical routine workup of patients undergoing revision surgery in our hospital. The study was approved by the local ethics committee and all patients consented to the use of their data.

Results

Preoperative data

The study population consisted of 18 patients who underwent a total of 20 revision surgeries. Eleven patients had persistent or recurrent PHPT, which was sporadic in nine patients, due to a MEN1 mutation in one patient, and due to parathyroid carcinoma in one patient. Seven patients had persistent or recurrent autonomous THPT due to end-stage renal failure. Patients had an average of two previous surgeries, during which an average of three pathological parathyroid glands were removed (Table 1).

Operative and pathological data

Surgical approach consisted of bilateral neck exploration in ten cases, unilateral neck exploration in eight cases, and a sternotomy in two cases. Bilateral neck exploration was extended to include mediastinal exploration via sternotomy in eight cases in which no pathological glands could be found after extensive exploration of the neck.

A single parathyroid adenoma was removed in five cases. In three of these five cases, this was a second adenoma, with an adenoma also removed at initial surgery. All of the three second adenomas were found in normal anatomical locations, in the right ($n=2$) or the left ($n=1$) lower quadrant of the neck. Cure was achieved in two of these three cases. In the other two cases, no pathological glands were removed at initial surgery, and both the adenomas were identified in ectopic locations, in the mediastinum ($n=1$), and high on the left side of the neck on the prevertebral fascia ($n=1$). Both of these revision surgeries resulted in cure.

One or more hyperplastic gland(s) ($n=14$) were removed in 12 cases. The majority of hyperplastic glands were identified in normal anatomical locations, in the left upper quadrant ($n=4$), left lower quadrant ($n=3$), right upper quadrant ($n=1$), or right lower quadrant ($n=3$) of the neck. Three glands were removed from ectopic locations, two were in the mediastinum and one was intrathyroidal. Only 5 of these 12 revision surgeries (42%) resulted in cure.

A metastasis of a parathyroid carcinoma was removed in one case, which resulted in cure lasting for more than 11 months. In the last two cases, extensive bilateral neck exploration failed to identify pathological parathyroid glands. Cure was thus achieved in 10 of the 18 patients with persistent or recurrent hyperparathyroidism, 5 after a second surgery, 4 after a third surgery, and 1 patient with parathyroid carcinoma was normocalcaemic for almost 1 year after his sixth surgery but has since developed recurrent hyperparathyroidism.

Predictive value of Tc99m-MIBI-SPECT

Tc99m-MIBI-SPECT scans performed before revision surgery were negative in 11 of 20 cases. Scans were only able to detect and accurately localize 6 of 20 surgically removed pathological glands and had thus a sensitivity of 30%.

SVS for PTH

An average number of 36 ± 8 samples were collected during each of the 20 SVS procedures. A positive gradient in PTH concentration of $> 50\%$ suggesting the presence of a hyperactive parathyroid gland was documented in all 20 cases. The median of the highest PTH concentration found at sampling was 35 pmol/l (range 16–2202 pmol/l) in patients with persistent or recurrent PHPT and 182 pmol/l (range 39–790 pmol/l) in patients with persistent or recurrent THPT ($P=0.8$). The average gradient was a fourfold increase in PTH concentration (range 1.5–9), which was not significantly different between the patient groups ($P=0.7$). There were no complications reported for any of the 20 sampling procedures.

Table 1 Demographic, laboratory, operative, and pathological data of patients who underwent Tc99m-MiBi-SPECT and selective venous sampling (SVS) for PTH prior to revision surgery for persistent or recurrent PHPT or autonomous THPT.

	Eleven patients with PHPT (13 operations)	Seven patients with THPT (7 operations)	P value
Age at time of SVS (years)	52±3	49±5	0.628
Sex (M/F)	4:7	3:4	0.528
Time after initial operation (months)	121±35	75±26	0.388
Previous operations (No)			
1	5	4	
2	3	2	
3+	5	1	
Glands removed at previous operations (No)			
0	2	0	
1	5	1	
2	1	1	
3+	5	5	
Pathological data at previous operations			
Adenoma	3/13 (23%)	2/7 (28%)	0.787
Hyperplasia	7/13 (54%)	5/7 (72%)	0.444
Carcinoma	1/13 (8%)	0	0.452
No pathological parathyroid glands	2/13 (15%)	0	0.274
Preoperative laboratory data			
Corrected s-calcium (mmol/l)	2.72±0.06	2.67±0.08	0.623
s-PTH (pmol/l)	48.9±31.8	50.6±14.7	0.971
Selective venous sampling			
Number of samples	36±3	36±2	0.966
Gradient of increase in PTH	4±0.5	4±1	0.745
Maximum PTH concentration (pmol/l)	214±166	277±106	0.797
Post-SVS operative data			
Bilateral neck exploration	8/13 (62%)	2/7 (29%)	0.160
Unilateral neck exploration	4/13 (31%)	4/7 (57%)	0.251
Sternotomy alone	1/13 (8%)	1/7 (14%)	0.639
Neck exploration combined with sternotomy	4/13 (31%)	2/7 (29%)	0.919
Post-SVS pathological data			
Adenoma	4/13 (31%)	1/7 (14%)	0.417
Hyperplasia	7/13 (54%)	5/7 (72%)	0.444
Carcinoma	1/13 (8%)	0	0.452
No pathological parathyroid glands	1/13 (8%)	1/7 (14%)	0.639

PHPT, primary hyperparathyroidism; THPT, tertiary hyperparathyroidism due to end-stage renal failure; s, serum; PTH, parathyroid hormone; No, number.

Sensitivity of SVS for localizing pathological parathyroid glands

SVS for PTH was able to accurately localize 15 of the 20 pathological parathyroid glands removed at 20 revision surgeries. Ten of these 15 glands, 7 hyperplastic glands and 3 adenomas, were found in normal anatomical locations in the left lower ($n=3$), right lower ($n=4$), and left upper ($n=3$) quadrants of the neck. Five of these 15 pathological parathyroid glands were found in ectopic locations: 4 in the mediastinum and 1 high on the left side of the neck on the prevertebral fascia.

All the five pathological parathyroid glands, which were not accurately localized by the SVS, were hyperplastic in nature with an average size of 7 mm. Four of these glands were removed from normal anatomical locations and one was intrathyroidal. In only two of these five glands was a gradient found on the correct side of the neck, but not in the correct quadrant.

Sensitivity of SVS in relation to parathyroid gland pathology

SVS was able to accurately localize all the 5 adenomas (100%), 9 of the 14 hyperplastic glands (64%), and 1 metastasis from a parathyroid carcinoma (100%) subsequently removed at surgery.

Sensitivity of SVS for pathological parathyroid glands in anatomically expected versus ectopic locations

SVS was able to accurately localize 10 of the 14 pathological glands found in normal anatomical locations (71%) and 5 of the 6 pathological glands found in ectopic locations (83%): mediastinum, $n=4$ and high on the left side of the neck on the prevertebral fascia, $n=1$.

A gradient in both the distal brachiocephalic and the left jugular vein ($n=2$) accurately corresponded to the finding of a pathological parathyroid gland in the neck at surgery in two cases (100%). A gradient in both

Figure 3 Flowchart of the outcome of Tc99m-MIBI-SPECT compared with SVS in 20 patients who underwent revision surgery.

the proximal brachiocephalic vein and the vena cava superior ($n=3$) accurately corresponded to a pathological gland in the right lower quadrant of the neck in two of the three cases (67%) and in one case no pathological gland could be found despite extensive neck and mediastinal exploration. A gradient in the vena cava superior and the azygos vein accurately corresponded to the presence of a gland in the mediastinum in two of the two cases (100%).

Sensitivity of SVS in relation to pathological parathyroid gland size

SVS was able to accurately localize 8 of the 9 pathological glands (89%) with a diameter > 1.5 cm, but only 6 of the 11 pathological glands (55%) with a diameter smaller than 1.5 cm, 9 of which were hyperplastic (82%).

Sensitivity of SVS for localizing pathological parathyroid glands compared with that of Tc99m-MIBI-SPECT

Tc99m-MIBI-SPECT and SVS were both performed prior to the 20 revision surgeries, during which 1 pathological parathyroid gland was removed in 16 patients, 2 pathological glands in 2 patients, and none in 2 patients despite extensive neck and mediastinal exploration. Of these 20 surgically excised glands, 15 (75%) were accurately localized by SVS compared with only 6 (30%) by Tc99m-MIBI-SPECT. SVS was thus able to accurately localize 10 of the 14 pathological glands (71%), which had been inaccurately localized or completely missed by Tc99m-MIBI-SPECT, while Tc99m-MIBI-SPECT was only able to localize 1 of the 6 pathological glands (17%) inaccurately localized by SVS.

Localization accuracy was highest when the outcome of Tc99m-MIBI-SPECT and SVS was concordant ($n=5$) (Fig. 3). The overall ability of SVS to accurately localize pathological glands was significantly higher than that of Tc99m-MIBI-SPECT ($P=0.012$).

Discussion

This study demonstrates the ability of SVS for PTH to accurately localize residual hyperactive parathyroid glands in patients with persistent or recurrent hyperparathyroidism is significantly higher than that of the noninvasive Tc99m-MIBI-SPECT imaging technique. To date, Tc99m-MIBI-SPECT and US of the neck are the most widely used imaging techniques with a sensitivity of up to 90% prior to initial surgery for PHPT (1–5, 7, 10, 35). However, the sensitivity of these techniques has been reported to be as low as 50% before revision surgery for persistent PHPT (15–17).

Owing to the invasive nature of SVS and the high costs of the procedure, SVS has been generally used only prior to revision surgery. In keeping with previous observations, this study shows the better performance of SVS in the accurate detection of residual pathological parathyroid tissue prior to revision surgery compared with that of the widely used Tc99m-MIBI-SPECT (15–17). In our hands, SVS was indeed able to accurately localize 71% of the pathological glands missed by Tc99m-MIBI-SPECT. Of significant relevance to the operating surgeon is the localizing sensitivity of 100% when concordance is achieved between SVS and Tc99m-MIBI-SPECT, compared with a sensitivity of only 30% when localization is only dependent on Tc99m-MIBI-SPECT.

The disappointing low predictive value of the Tc99m-MIBI-SPECT imaging technique in patients with persistent PHPT is believed to be due to the usually small size of residual parathyroid glands and to their frequent hyperplastic nature (1, 6, 35–38). Our findings suggest that the sensitivity of SVS is also decreased in the case of pathological parathyroid glands smaller than 1.5 cm compared with glands >1.5 cm (55 vs 89%) and in the case of hyperplastic compared with adenomatous residual glands (64 vs 100%), hyperplastic glands being smaller than adenomatous ones (1.45 vs 2.3 cm; $P=0.21$). Although gland size could potentially influence the predictive value of SVS by determining the amount of PTH secreted by the hyperactive parathyroid gland, we were unable to demonstrate a correlation between the gradient in PTH concentration as measured at SVS and the size of the pathological parathyroid gland removed at surgery.

One of the most frequently reported causes of persistent hyperparathyroidism is an ectopic mediastinal location of a pathological parathyroid gland (11, 39). Our data and those of others demonstrate a high sensitivity of SVS ranging from 66 to 100% for the localization of these ectopically located glands (17, 40). In keeping with previous reports (22), we also observed that SVS was able to accurately localize all ectopically located pathological glands in the mediastinum by the finding of a gradient in the superior vena cava (SVC) alone, or by the finding of a simultaneous gradient in the SVC and in the azygos vein and/or in the brachiocephalic vein. A PTH gradient found only in the brachiocephalic vein remains, however, an interpretational challenge. In contrast to Nilsson *et al.* (22), who suggested that a gradient in the proximal brachiocephalic vein or the SVC corresponded to a mediastinal parathyroid gland in all cases, we observed that a simultaneous gradient in the SVC as well as in the azygos vein was necessary for conclusive evidence for a hyperactive parathyroid gland in the mediastinum. A gradient in the distal brachiocephalic vein was less specific in the study reported by Nilsson *et al.* (22), corresponding to a mediastinal gland in 86% of cases and to a cervical gland in 14% of cases. Our data suggest, however, that a gradient in the distal brachiocephalic vein corresponded to the localization of a pathological gland on the left side of the neck in 100% of cases.

In persistent or recurrent hyperparathyroidism, previous surgeries may disturb the venous anatomy, which jeopardize the localizing ability of radiotracer techniques, such as Tc99m-MIBI-SPECT, and sometimes lead to challenging interpretation of venous sampling data. Notwithstanding, our findings demonstrate that in patients with persistent or recurrent hyperparathyroidism the ability of SVS for PTH to detect and accurately localize pathological parathyroid glands is significantly higher than that of the widely used Tc99m-MIBI-SPECT imaging technique. In experienced hands, the SVS procedure is safe and devoid of complications. Concordance of both techniques leads to a reassuring

sensitivity of 100%. Our data from this study clearly suggest that SVS for PTH should be reinstated as a valuable tool in the armamentarium of localization studies in the preoperative workup of patients with persistent or recurrent hyperparathyroidism.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

References

- 1 Jones JM, Russell CF, Ferguson WR & Laird JD. Pre-operative sestamibi-technetium subtraction scintigraphy in primary hyperparathyroidism: experience with 156 consecutive patients. *Clinical Radiology* 2001 **56** 556–559. (doi:10.1053/crad.2001.0701)
- 2 Chiu B, Sturgeon C & Angelos P. What is the link between nonlocalizing sestamibi scans, multigland disease, and persistent hypercalcemia? A study of 401 consecutive patients undergoing parathyroidectomy. *Surgery* 2006 **140** 418–422. (doi:10.1016/j.surg.2006.03.021)
- 3 Calva-Cerqueira D, Smith BJ, Hostetler ML, Lal G, Menda Y, O'Dorisio TM & Howe JR. Minimally invasive parathyroidectomy and preoperative MIBI scans: correlation of gland weight and preoperative PTH. *Journal of the American College of Surgeons* 2007 **205** S38–S44. (doi:10.1016/j.jamcollsurg.2007.06.322)
- 4 Palmer RM & Lokey JS. Is minimally invasive parathyroidectomy reasonable in the nonuniversity setting? *American Journal of Surgery* 2006 **192** 865–868. (doi:10.1016/j.amjsurg.2006.08.059)
- 5 Bergenfelz A, Lindblom P, Tibblin S & Westerdahl J. Unilateral versus bilateral neck exploration for primary hyperparathyroidism: a prospective randomized controlled trial. *Annals of Surgery* 2002 **236** 543–551. (doi:10.1097/0000658-200211000-00001)
- 6 Westerdahl J & Bergenfelz A. Sestamibi scan-directed parathyroid surgery: potentially high failure rate without measurement of intraoperative parathyroid hormone. *World Journal of Surgery* 2004 **28** 1132–1138. (doi:10.1007/s00268-004-7484-3)
- 7 Moka D, Voth E, Dietlein M, Larena-Avellaneda A & Schicha H. Technetium 99m-MIBI-SPECT: a highly sensitive diagnostic tool for localization of parathyroid adenomas. *Surgery* 2000 **128** 29–35. (doi:10.1067/msy.2000.107066)
- 8 Goldstein RE, Billheimer D, Martin WH & Richards K. Sestamibi scanning and minimally invasive radioguided parathyroidectomy without intraoperative parathyroid hormone measurement. *Annals of Surgery* 2003 **237** 722–730. (doi:10.1097/0000658-200305000-00015)
- 9 Udelsman R. Six hundred fifty-six consecutive explorations for primary hyperparathyroidism. *Annals of Surgery* 2002 **235** 665–670. (doi:10.1097/0000658-200205000-00008)
- 10 Ruda JM, Hollenbeak CS & Stack BC Jr. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. *Otolaryngology and Head and Neck Surgery* 2005 **132** 359–372. (doi:10.1016/j.otohns.2004.10.005)
- 11 Shen W, Duren M, Morita E, Higgins C, Duh QY, Siperstein AE & Clark OH. Reoperation for persistent or recurrent primary hyperparathyroidism. *Archives of Surgery* 1996 **131** 861–867.

- 12 Hasse C, Sitter H, Brune M, Wollenteit I, Nies C & Rothmund M. Quality of life and patient satisfaction after reoperation for primary hyperparathyroidism: analysis of long-term results. *World Journal of Surgery* 2002 **26** 1029–1036. (doi:10.1007/s00268-002-6664-2)
- 13 Gough I. Reoperative parathyroid surgery: the importance of ectopic location and multigland disease. *ANZ Journal of Surgery* 2006 **76** 1048–1050. (doi:10.1111/j.1445-2197.2006.03931.x)
- 14 Carty SE & Norton JA. Management of patients with persistent or recurrent primary hyperparathyroidism. *World Journal of Surgery* 1991 **15** 716–723. (doi:10.1007/BF01665305)
- 15 Rotstein L, Irish J, Gullane P, Keller MA & Sniderman K. Reoperative parathyroidectomy in the era of localization technology. *Head & Neck* 1998 **20** 535–539. (doi:10.1002/(SICI)1097-0347(199809)20:6<535::AID-HED8>3.0.CO;2-8)
- 16 Chen CC, Skarulis MC, Fraker DL, Alexander R, Marx SJ & Spiegel AM. Technetium-99m-sestamibi imaging before reoperation for primary hyperparathyroidism. *Journal of Nuclear Medicine* 1995 **36** 2186–2191.
- 17 Fayet P, Hoeffel C, Fulla Y, Legmann P, Hazebroucq V, Luton JP, Chapuis Y, Richard B & Bonnin A. Technetium-99m sestamibi scintigraphy, magnetic resonance imaging and venous blood sampling in persistent and recurrent hyperparathyroidism. *British Journal of Radiology* 1997 **70** 459–464.
- 18 Numerow LM, Morita ET, Clark OH & Higgins CB. Persistent/recurrent hyperparathyroidism: a comparison of sestamibi scintigraphy, MRI, and ultrasonography. *Journal of Magnetic Resonance Imaging* 1995 **5** 702–708. (doi:10.1002/jmri.1880050614)
- 19 Peeler BB, Martin WH, Sandler MP & Goldstein RE. Sestamibi parathyroid scanning and preoperative localization studies for patients with recurrent/persistent hyperparathyroidism or significant comorbid conditions: development of an optimal localization strategy. *American Surgeon* 1997 **63** 37–46.
- 20 Dunlop DA, Papapoulos SE, Lodge RW, Fulton AJ, Kendall BE & O'Riordan JL. Parathyroid venous sampling: anatomic considerations and results in 95 patients with primary hyperparathyroidism. *British Journal of Radiology* 1980 **53** 183–191. (doi:10.1259/0007-1285-53-627-183)
- 21 Sugg SL, Fraker DL, Alexander R, Doppman JL, Miller DL, Chang R, Skarulis MC, Marx SJ, Spiegel AM & Norton JA. Prospective evaluation of selective venous sampling for parathyroid hormone concentration in patients undergoing reoperations for primary hyperparathyroidism. *Surgery* 1993 **114** 1004–1009.
- 22 Nilsson BE, Tisell LE, Jansson S, Zackrisson BF, Lindstedt G & Lundberg PA. Parathyroid localization by catheterization of large cervical and mediastinal veins to determine serum concentrations of intact parathyroid hormone. *World Journal of Surgery* 1994 **18** 605–610. (doi:10.1007/BF00353777)
- 23 Winzelberg GG & Hydovitz JD. Radionuclide imaging of parathyroid tumors: historical perspectives and newer techniques. *Seminars in Nuclear Medicine* 1985 **15** 161–170. (doi:10.1016/S0001-2998(85)80024-6)
- 24 Reidel MA, Schilling T, Graf S, Hinz U, Nawroth P, Buchler MW & Weber T. Localization of hyperfunctioning parathyroid glands by selective venous sampling in reoperation for primary or secondary hyperparathyroidism. *Surgery* 2006 **140** 907–913. (doi:10.1016/j.surg.2006.06.037)
- 25 Mariette C, Pellissier L, Combemale F, Quievreux JL, Carnaille B & Proye C. Reoperation for persistent or recurrent primary hyperparathyroidism. *Langenbeck's Archives of Surgery* 1998 **383** 174–179. (doi:10.1007/s004230050113)
- 26 Jaskowiak N, Norton JA, Alexander HR, Doppman JL, Shawker T, Skarulis M, Marx S, Spiegel A & Fraker DL. A prospective trial evaluating a standard approach to reoperation for missed parathyroid adenoma. *Annals of Surgery* 1996 **224** 308–320. (doi:10.1097/0000658-199609000-00007)
- 27 Jones JJ, Brunaud L, Dowd CF, Duh QY, Morita E & Clark OH. Accuracy of selective venous sampling for intact parathyroid hormone in difficult patients with recurrent or persistent hyperparathyroidism. *Surgery* 2002 **132** 944–950. (doi:10.1067/msy.2002.128477)
- 28 Yen TW, Wang TS, Doffek KM, Krzywda EA & Wilson SD. Reoperative parathyroidectomy: an algorithm for imaging and monitoring of intraoperative parathyroid hormone levels that results in a successful focused approach. *Surgery* 2008 **144** 611–619. (doi:10.1016/j.surg.2008.06.017)
- 29 Estella E, Leong MS, Bennett I, Hartley L, Wetzig N, Archibald CA, Harper JS & Cuneo RC. Parathyroid hormone venous sampling prior to reoperation for primary hyperparathyroidism. *ANZ Journal of Surgery* 2003 **73** 800–805. (doi:10.1046/j.1445-2197.2003.02678.x)
- 30 Satava RM Jr, Beahrs OH & Scholz DA. Success rate of cervical exploration for hyperparathyroidism. *Archives of Surgery* 1975 **110** 625–628.
- 31 Hessman O, Stalberg P, Sundin A, Garske U, Rudberg C, Eriksson LG, Hellman P & Akerstrom G. High success rate of parathyroid reoperation may be achieved with improved localization diagnosis. *World Journal of Surgery* 2008 **32** 774–781. (doi:10.1007/s00268-008-9537-5)
- 32 Clark OH, Okerlund MD, Moss AA, Stark D, Norman D, Newton TH, Duh QY, Arnaud CD, Harris S & Gooding GA. Localization studies in patients with persistent or recurrent hyperparathyroidism. *Surgery* 1985 **98** 1083–1094.
- 33 Witteveen JE, Kievit J, Morreau H, Romijn JA & Hamdy NA. No recurrence of sporadic primary hyperparathyroidism when cure is established 6 months after parathyroidectomy. *European Journal of Endocrinology* 2010 **162** 399–406. (doi:10.1530/EJE-09-0789)
- 34 Ito F, Sippel R, Lederman J & Chen H. The utility of intraoperative bilateral internal jugular venous sampling with rapid parathyroid hormone testing. *Annals of Surgery* 2007 **245** 959–963. (doi:10.1097/01.sla.0000255578.11198.8f)
- 35 Carneiro-Pla DM, Solorzano CC & Irvin GL III. Consequences of targeted parathyroidectomy guided by localization studies without intraoperative parathyroid hormone monitoring. *Journal of the American College of Surgeons* 2006 **202** 715–722. (doi:10.1016/j.jamcollsurg.2006.02.003)
- 36 Mihai R, Gleeson F, Buley ID, Roskell DE & Sadler GP. Negative imaging studies for primary hyperparathyroidism are unavoidable: correlation of sestamibi and high-resolution ultrasound scanning with histological analysis in 150 patients. *World Journal of Surgery* 2006 **30** 697–704. (doi:10.1007/s00268-005-0338-9)
- 37 Lumachi F, Zucchetta P, Marzola MC, Boccagni P, Angelini F, Bui F, D'Amico DF & Favia G. Advantages of combined technetium-99m-sestamibi scintigraphy and high-resolution ultrasonography in parathyroid localization: comparative study in 91 patients with primary hyperparathyroidism. *European Journal of Endocrinology* 2000 **143** 755–760. (doi:10.1530/eje.0.1430755)
- 38 Allendorf J, Kim L, Chabot J, DiGiorgi M, Spanknebel K & LoGerfo P. The impact of sestamibi scanning on the outcome of parathyroid surgery. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 3015–3018. (doi:10.1210/jc.2002-021095)
- 39 McIntyre RC Jr, Kumpe DA & Liechty RD. Reexploration and angiographic ablation for hyperparathyroidism. *Archives of Surgery* 1994 **129** 499–503.
- 40 Rodriguez JM, Tezelman S, Siperstein AE, Duh QY, Higgins C, Morita E, Dowd CF & Clark OH. Localization procedures in patients with persistent or recurrent hyperparathyroidism. *Archives of Surgery* 1994 **129** 870–875.

Received 24 August 2010

Accepted 24 September 2010